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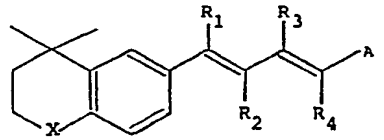
(56) & (58) continued overleaf

(54) New chroman and thiochroman derivatives

(57) A chroman or thiochroman derivative which is a compound of formula (I):



(I)

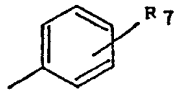
wherein:

X is −O− or −S−;

R_1, R_2, R_3 and R_4 are each independently, hydrogen or a C_1-C_6 alkyl group; and

A is:

a) a group of formula (II):



(II)

wherein R_7 is:

a group of formula (III):

$-CH_2OR_8$ (III)

wherein R_8 is:

hydrogen;

a C_1-C_6 alkyl group; or

a C_2-C_6 mono- or polyhydroxyalkyl group;

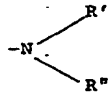
a group of formula (IV):

(IV)

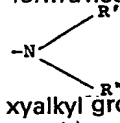
wherein R_9 is:

hydrogen;

a C_1-C_6 alkyl group;

a group of formula 

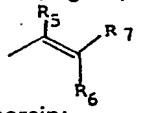
wherein R′ and R″ are each, independently, hydrogen, a C_1-C_6 alkyl group or a C_3-C_6 alkenyl group or wherein R′ and R″ form a heterocyclic system together with the nitrogen atom to which they are attached, or wherein the group



is an amino acid residue or an amino sugar residue; or

a group of formula $-O-R_{10}$, wherein R_{10} is hydrogen, a C_1-C_{20} alkyl group or a C_2-C_6 mono- or polyhydroxyalkyl group or wherein $-O-R_{10}$ is derived from a sugar; or

b) a group of formula (V)



(V)

wherein:

R_5 and R_6 are each, independently, hydrogen or a C_1-C_6 alkyl group; or a salt thereof is useful in *cosmetic* and *medicinal compositions*.

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(71) Applicant
L'Oreal,

(Incorporated in France),

14 rue Royale, 75008 Paris, France

(72) Inventors
Gerard Lang,
Guy Solladie,
Serge Forestier,
Alain Lagrange

(74) Agent and/or Address for Service
J. A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5EU

(56) Documents cited
None

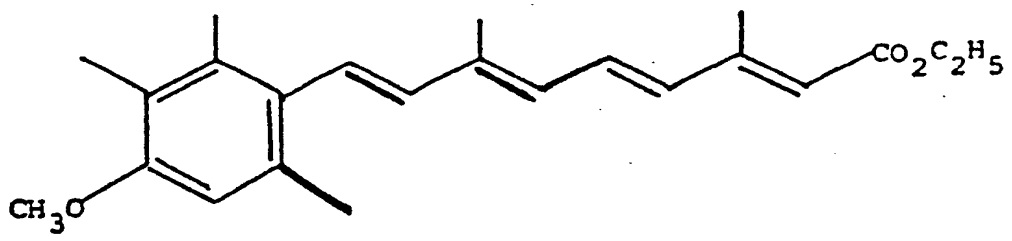
(58) Field of search
C2C

SPECIFICATION

New chroman and thiochroman derivatives, the process for preparing them and medicinal and cosmetic compositions containing them

The present invention relates to new chroman and thiocroman derivatives, to processes for their preparation and to the use of these derivatives in cosmetics, or in human and veterinary medicine as pharmaceutical preparations.

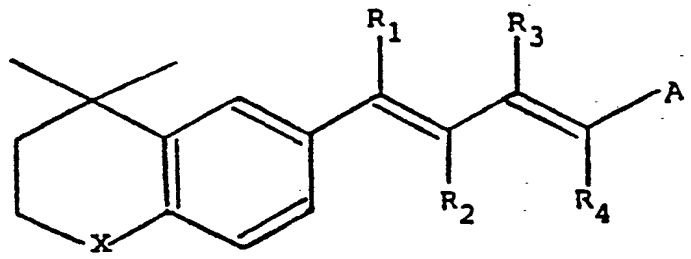
The therapeutic action of vitamin A in its acid, aldehyde or alcohol form is well known in dermatology [in this connection, see the publication EXPERIENTIA, volume *34*, pages 1105–1119 (1978)]; this action in the treatment of cutaneous proliferations, acne, psoriasis and similar conditions will be designated hereinafter by the generic term "retinoid type action". It was found that products having a structure analogous to vitamin A also showed a retinoid type action, but that the side effect of toxic hypervitaminosis could, for certain compounds, be boosted by a smaller factor than the boosting factor of the retinoid effect sought [in this connection, see EUR. J. MED. CHEM. – CHIMICA THERAPEUTICA, January–February 1980, 15, No. 1, pages 9–15]. In this latter publication, P. Loeliger et al. described a compound of formula (a):



(a)

We have surprisingly found that the benzene ring of compounds such as those shown above can be replaced by a chroman or thiochroman ring-system and that other substitutions can be introduced on the side chain without losing the benefit of the retinoid type action.

Accordingly the present invention provides a chroman or thiochroman derivative which is a compound of formula (I):



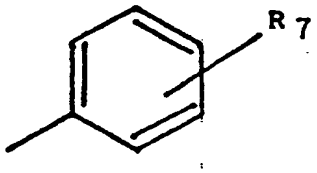
(I)

wherein

X is –O– or –S–;

R_1, R_2, R_3 and R_4 are each, independently, hydrogen or a linear or branched C_1–C_6 alkyl group; and A is:

A) a group of formula (II):



(II)

wherein R_7 is:

a group of formula (III):

$$-CH_2OR_8 \qquad \text{(III)}$$

wherein R_8 is:

hydrogen;

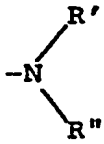
a C_1–C_6 alkyl group; or

a C_2–C_6 mono- or polyhydroxyalkyl group;

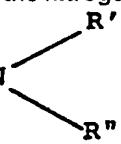
a group of formula (IV):

(IV)

wherein R_9 is:
hydrogen;
a C_1–C_6 alkyl group;

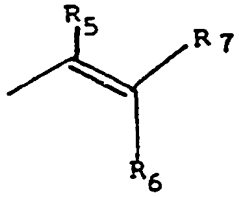


a group of formula wherein R′ and R″ are each independently, hydrogen, a C_1–C_6 alkyl group or a C_3–C_6 alkenyl group or wherein R′ and R″ form a heterocyclic system together with the nitrogen atom to which they are attached, or wherein the group



is an amino acid resiude or an amino sugar residue; or a group of formula –0–R_{10}, wherein R_{10} is hydrogen, a C_1–C_{20} alkyl group or a C_2–C_6 mono- or polyhydroxyalkyl group or wherein –OR_{10} is derived from a sugar; or

b) a group of formula (V):



(V)

wherein:
R_7 is as defined above; and
R_5 and R_6 are each, independently, hydrogen or a linear or branched C_1–C_6 alkyl group;
or a salt thereof, including their geometrical and optical isomers.

Preferred C_1–C_6 alkyl groups represented by R_1 to R_6, R_8, R_9, R′ and R″ are methyl, ethyl, isopropyl, butyl and tert-butyl groups, R_1 to R_6 are preferably methyl groups.

Preferred C_1–C_{20} alkyl groups represented by R_{10} are methyl, ethyl, proply, 2-ethylhexyl, octyl, dodecyl, hexadecyl and octadecyl groups.

Preferred C_2–C_6 mono- or polyhydroxyalkyl groups represented by R_{10} are a 2-hydroxyethyl or 2,3-dihydroxypropyl groups or a pentaerythritol residue.

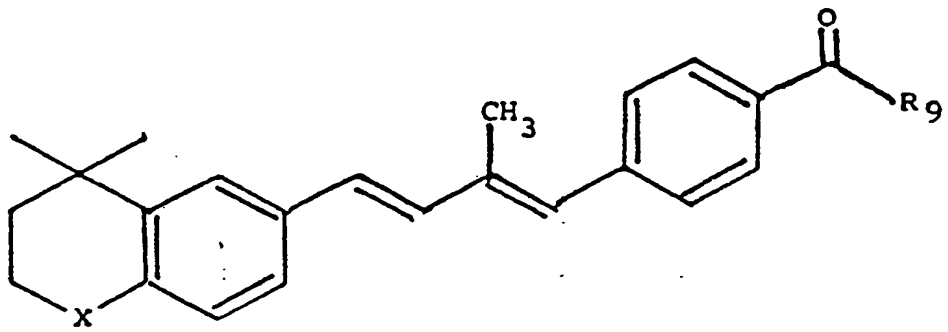
Preferred C_3–C_6 alkenyl groups represented by R′ and R″ are propenyl, butenyl and isopentenyl groups.

When R′ and R″ form a heterocyclic system together with the nitrogen atom to which they are attached, the system is preferably a piperidino, morpholino, piperazino, pyrrolidino or 4-(2-hydroxyethyl)piperazino group.

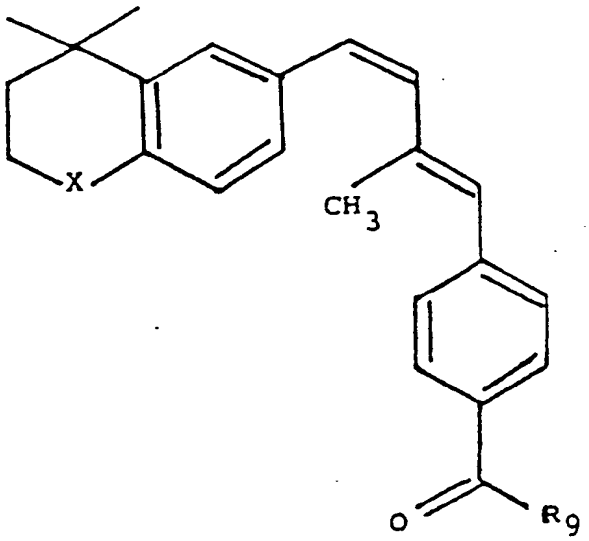
If the group –OR_{10} is derived from a sugar, the sugar may be, for example, glucose, mannitol or erythritol.

The salts of the compounds of formula (I), including their isomers may, for example, be zinc, alkali metal, alkaline earth metal, or organic amine salts of compounds of formula (I) when they contain at least one free acid group, or salts of an inorganic or organic acid, in particular hydrochloride, hydrobromide or citrate, when they contain at least one amine group.

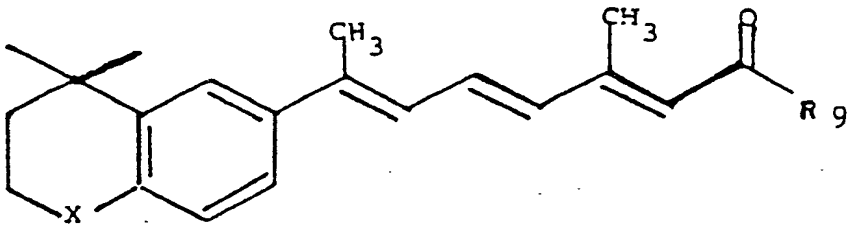
Especially preferred derivatives include those of the following formulae:



(Ia)

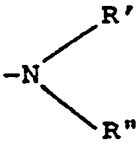


(Ib)



(Ic)

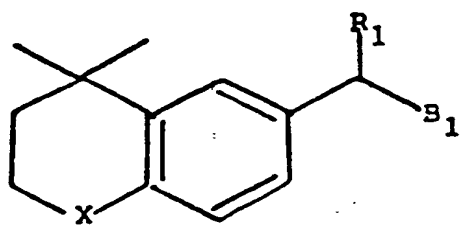
wherein
X is –O– or –S–;

R_9 is a group of formula 

wherein
R′ and R″ are each, independently, hydrogen or a C_1–C_6 alkyl group or R_9 is a group of formula –O–R_{10} wherein R_{10} is hydrogen, a C_1–C_{20} alkyl group or a C_2–C_6 mono- or polyhydroxyalkyl group.

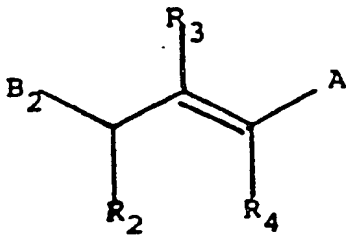
Preferred compounds of formula (I) include:
6-[(1E,3E)-4-(4-methoxycarbonylphenyl)-3–methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1E,3E)-4-(4-methoxycarbonylphenyl)-3–methyl-1,3-butadienyl]-4,4-dimethylthiochroman;
6-[(1E,3E)-4-(4-carboxyphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1E,3E)-4-(4-carboxyphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylthiochroman;
6-[(1E,3E)-4-(4-ethylaminocarbonylphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1Z,3E)-4-(4-methoxycarbonylphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1Z,3E)-4-(4-methoxycarbonylphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylthiochroman;
6-[(1Z,3E)-4-(4-carboxyphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1Z,3E)-4-(4-carboxyphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylthiochroman;
6-[(1E,3E,5E)-6-ethoxycarbonyl-1,5-dimethyl-1,3-5-hexatrienyl]-4,4-dimethylchroman; and
6-[(1E,3E,5E)-6-carboxy-1,5-dimethyl-1,3,5-hexatrienyl]-4,4-dimethylchroman.

The present invention also provides a process for preparing a derivative as defined above wherein a compound of formula (VI):



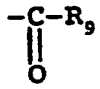
(VI)

is reacted with a compound of formula (VII):



(VII)

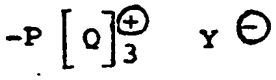
wherein R_1, R_2, R_3, R_4 and A are as defined above with the proviso that R_7 is not a group of formula (IV):



(IV)

when R_9 is hydrogen or a C_1–C_6 alkyl group, and wherein one of the groups B_1 and B_2 is an oxo group and the other is:

a) a triarylphosphonium group of formula (VIII)



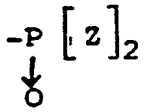
(VIII)

wherein:

Q is an aryl group; and

Y is a monovalent anion of an organic or inorganic acid; or

b) a dialkoxyphosphinyl group of formula (IX):



(IX)

wherein Z is a C_1–C_6 alkoxy group.

In the case where one of B_1 and B_2 is an oxo group and the other is a triarylphosphonium group of formula (VIII), the reaction is preferably performed in the presence of an alkali metal alcoholate such as sodium methylate, in the presence of an alkali metal hydride such as sodium hydride, or in the presence of butyllithium, in a solvent such as tetrahydrofuran or dimethylformamide, in the presence of an alkali metal carbonate such as potassium carbonate, in an alcohol such as isopropanol, or in the presence of an alkylene oxide optionally substituted with an alkyl group, optionally in a solvent such as dichloromethane, the reaction temperature preferably being from −80°C to the boiling point of the reaction mixture.

When one of B_1 and B_2 is an oxo group and the other is a dialkoxyphosphinyl group of formula (IX), the reaction is preferably performed in the presence of a base, preferably, in the presence of an inert organic solvent, for example by means of sodium hydride in benzene, toluene, dimethylformamide, tetrahydrofuran, dioxane or 1,2-dimethoxyethane, or by means of an alcoholate, for example by means of sodium methylate, in methanol. The reaction may also be carried out using an inorganic base such as potassium hydroxide or sodium hydroxide, in an organic solvent such as tetrahydrofuran, or by means of an alkali metal carbonate, for example by means of potassium carbonate in water, or by means of butyllithium in tetrahydrofuran. It is also possible to add to the reaction mixture a crown ether capable of complexing the metal cation present in the base, and thereby enabling the strength of the latter to be increased. The reaction temperature is generally from −80°C to the boiling point of the reaction mixture.

The compounds of formulae (VI) and (VII) are known compounds or compounds which can be prepared by known methods.

The chroman or thiochroman derivative may undergo functional modification of the substituent R_7, such as the saponification of a carboxylic acid ester or the reduction of the carboxylic acid ester group to a hydroxymethyl group. The hydroxymethyl group can also be oxidised to a formyl group, or alternatively esterified or etherified. The carboxyl group can also be converted to a salt, an ester, an amide, an alcohol, an acetyl group or a corresponding acid chloride. A carboxylic acid ester group can be converted to an acetyl group. The acetyl group can be converted to a secondary alcohol group by reduction, and the secondary alcohol group can itself by alkylated or acylated by known procedures. All these functional modifications can be carried out by procedures which are known per se.

The derivatives of the present invention are usually obtained in a cis/trans mixture which can be separated,

if so desired, in a manner known per se, into the pure cis or trans type compounds.

The derivatives of the present invention possess an activity ranging from "good" to "excellent" in the test of inhibition of ornithine decarboxylase after induction by "tape stripping" in nude rats [M. Bouclier et al. Dermatologica, p. 169, No. 4 (1984)]. This test is accepted as a measure of the action of retinoids on cellular proliferation phenomena.

The derivatives of the present invention also possess enhanced activity in the test of differentiation of mouse embryonic teratocarcinoma cells (F9 cells: Cancer Research *43* p. 5268, 1983).

These derivatives are especially well suited to the treatment of dermatological conditions linked to a disorder of keratinization (differentiation, proliferation), as well as dermatological or other conditions having an inflammatory and/or immuno-allergic component, in particular:

acne vulgaris, comedonic or polymorphic acnes, senile acnes, acne solaris and acne medicamentosa or trade acnes;

extensive and/or severe forms of psoriasis, and other disorders of keratinization, in particular, ichthyoses and ichthyosiform states;

Darier's disease;

keratoderma palmaris et plantaris;

leukoplakia and leukoplakiform states, lichen planus; and

all benign or malignant, severe or extensive dermatological proliferations.

They can also be recommended in epidermolysis bullosa dystrophica and in diseases involving molecular changes in collagen. They also find application in ultra-violet-induced carcinomas (solar carcinogenesis) and in epidermodysplasia verruciformis and related forms.

They are also active for certain rheumatic conditions, in particular psoriatic rheumatism, and also in the treatment of atopy, whether cutaneous or respiratory. These compounds also find application in the treatment of degenerative diseases of connective tissue and tumours and in the ophthalmological field, in particular in the treatment of corneopathies.

The present invention therefore also provides a medicinal composition comprising a derivative as defined above and a pharmaceutically acceptable vehicle.

The medicinal composition is preferably in a form suitable for treatment of any one of the abovementioned conditions.

The derivatives of the present invention are generally administered at a daily dose of approximately 2 μ/kg to 2 mg/kg of bodyweight of the intended recipient.

The pharmaceutically acceptable vehicle can be any conventional vehicle, the active derivative preferably being either in the dissolved state or in the dispersed state in the vehicle.

The compositions of the present invention can, for example, be administered enterally, parenterally, topically or by application to the eye. For enteral administration, the medicinal substances preferably takes the form of tablets, gelatin capsules, dragées, syrups, suspensions, solutions, powders, granules or emulsions. For parenteral administration, the compositions may take the form of solutions or suspensions for perfusion or injection.

For topical administration, the compositions generally take the form of ointments, tinctures, creams, pomades, powders, patches, impregnated pads, solutions, lotions, gels, sprays or alternatively suspensions or emulsions. These compositions preferably contain from 0.0005 to approximately 2% by weight of the derivatives based on the total weight of the composition.

The compositions which can be used topically can be in either an anhydrous or aqueous form, according to the clinical indication.

For application to the eye, the compositions are generally eye lotions.

The derivatives of the present invention also find application in the cosmetic field, especially in body and hair hygiene and, in particular, in the treatment of skin which tends to be affected by acne, for promoting regrowth of the hair or acting against hair loss, for combating the greasy appearance of the skin or hair and also for the treatment of physiologically dry skin. They also can have a preventive and curative power against the deleterious effects of sunlight.

The present invention therefore also provides a cosmetic composition comprising at least one derivative as defined above and a cosmetically acceptable vehicle. This composition is preferably in the form of a lotion, gel, cream, soap or shampoo.

The concentration of derivatives of the present invention in the cosmetic composition is generally from 0.0005 to 2% by weight, and preferably from 0.01 to 1% by weight, based on the total weight of the composition.

The medicinal and cosmetic compositions of the present invention may contain inert, pharmacodynamically or cosmetically active additives, and in particular; moisturizing agents, such as thiamorpholinone and its derivatives or urea; anti-seborrhoeic or anti-acne agents, such as S-carboxymethylcysteine and S-benzylcysteamine and their derivatives, tioxolone or alternatively benzoyl peroxide; antibiotics, such as erythromycin and its esters, neomycin, tetracyclines or 4,5-polymethylene-3-isothiazolinones; agents promoting regrowth of the hair, such as minoxidil (2,4-diamino-6-piperidinopyrimidine-3-oxide) and its derivatives, anthralin and its derivatives, diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine-1,1-dioxide) and phenytoin (5,5-diphenylimidazolidine-2,4-dione); steroid and non-steroid anti-inflammatory agents; carotenoids, and in particular β-carotene; and anti-psoriatic agents such as anthralin and its derivatives and eicosa-5,8,11,14-

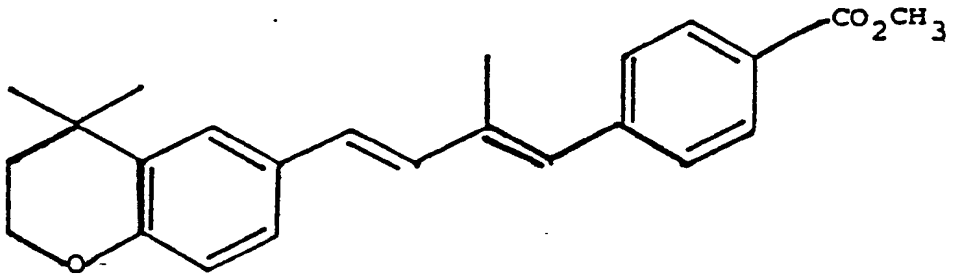
tetraynoic and 5,8,11-triynoic acids, their esters and their amides.

The compositions of the present invention may also contain flavour-improving agents, preservatives, stabilizers, moisture-regulating agents, pH-regulating agents, osmotic pressure-modifying agents, emulsifiers, UV-A and UV-B filters and antioxidants such as α-tocopherol, butylated hydroxyanisole or butylated hydroxytoluene.

The present invention is now further described in the following Examples.

EXAMPLE 1

Preparation of a compound of formula:



a) 4.85 g of 4,4,6-trimethylchroman are dissolved in 150 cm^3 of anhydrous carbon tetrachloride. 5 g of N-bromosuccinimide and 0.05 g of azobisisobutyronitrile are added. The mixture is heated for one hour under reflux with UV irradiation. After cooling, the succinimide formed is filtered off and the solution is washed with 150 cm^3 of saturated sodium bicarbonate solution. After the organic phase is dried, the solvent is evaporated off. 4.59 g of 6-bromomethyl-4,4-dimethylchroman are obtained.

b) 5.8 g of 6-bromomethyl-4,4-dimethylchroman obtained above are dissolved in 150 cm^3 of toluene. 6.6 g of triphenylphosphine are added. The reaction mixture is heated to 100°C for 6 hours. After evaporation of the solvent, the solid residue is reduced to a powder and washed several times with ether. 10.64 g of [(4,4-dimethyl-6-chromanyl)methyl]triphenylphosphonium bromide are obtained in the form of a white powder.

c) 15.4 g of the phosphonium bromide obtained above are suspended in 250 cm^3 of anhydrous tetrahydrofuran. 1.1 equivalent of n-butyllithium, in 1.6 N solution in hexane, is added at 0°C. After 15 minutes at 0°C, the excess butyllithium is destroyed by adding 20 cm^3 of anhydrous dichloromethane. The mixture is then cooled to −78°C and 0.95 equivalent of 3-(4-methoxycarbonylphenyl)-2-methyl-2-propenal, dissolved in 15 cm^3 of anhydrous dichloromethane, is added while the mixture is shielded from the light. The mixture is left to react for 30 min at −78°C, and the temperature is finally allowed to rise to room temperature in the course of 2 hours. The reaction mixture is poured into 200 cm^3 of saturated ammonium chloride solution. After dilution with 50 cm_3 of water, the aqueous solution is extracted with 2 times 100 cm^3 of ether. The organic phase is dried over sodium sulphate and filtered rapidly on silica gel. After evaporation of the solvent and recrystallization in hexane, 3.58 g of expected product are obtained, possessing the following properties:

melting point: 113°C

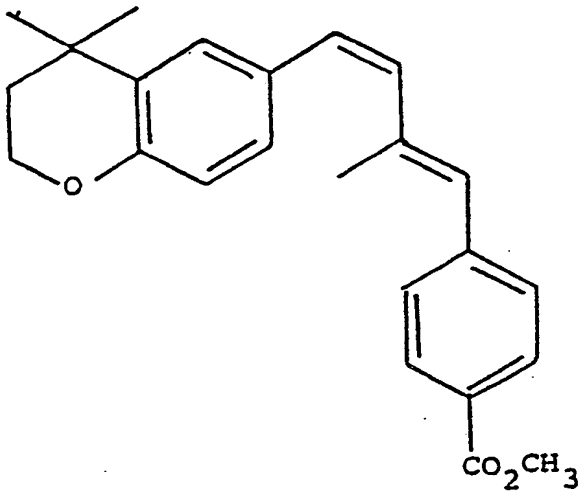
the ^1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) corresponds to the expected structure.

elementary analysis:

	C	*H*
calculated for $C_{24}H_{26}O_3$	79.53	7.23
found	79.69	7.37

EXAMPLE 2

Preparation of a compound of formula:



This compound is obtained from the mother liquors of recrystallization of the compound of Example 1c.

It possesses the following properties:

melting point: 83°C

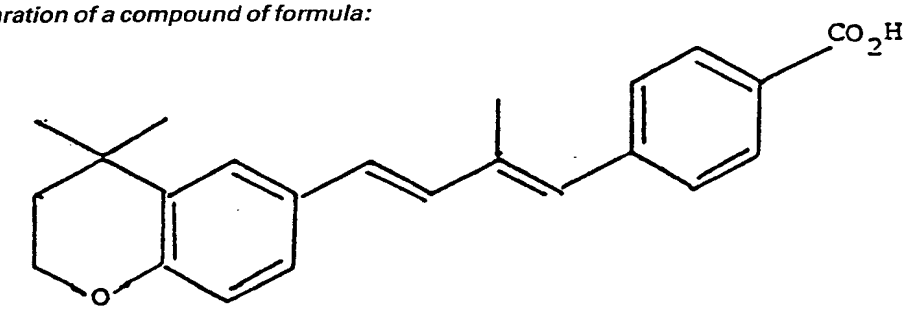
the ^1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) corresponds to the expected structure.

elementary analysis:

	C	*H*
calculated for $C_{24}H_{26}O_3$	79.53	7.23
found	79.77	7.51

EXAMPLE 3

Preparation of a compound of formula:



2.17 g of the compound obtained in Example 1c are heated for one hour at 50°C in a mixture containing 70 cm^3 of water, 50 cm^3 of ethanol and 20 g of sodium hydroxide. After being cooled, the mixture is diluted by adding 300 cm^3 of water and the ethanol is distilled off under reduced pressure. The residual aqueous solution is acidified to pH 2 with 10% strength hydrochloric acid solution. The acid, which precipitates, is filtered, and then washed with water. After recrystallization in acetone, the expected product is obtained in the form of a yellow solid, possessing the following properties:

melting point: 188°C (with decomposition)

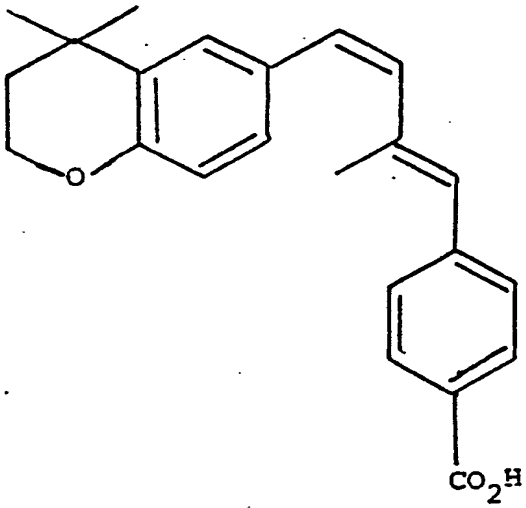
the ^1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) corresponds to the expected structure.

elementary analysis:

	C	*H*
calculated for $C_{23}H_{24}O_3$	79.28	6.94
found	79.20	7.02

EXAMPLE 4

Preparation of a compound of formula:



This compound is obtained according to the procedure described in Example 3, in which the compound of Example 1c is replaced by the compound of Example 2. After recrystallization in acetone, the expected product is obtained in the form of a yellow solid, possessing the following properties:

melting point: 150°C (with decomposition)

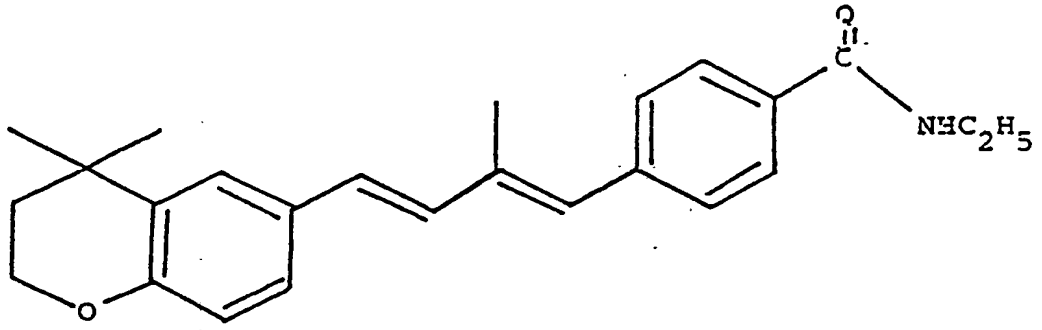
the 1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) corresponds to the expected structure.

elementary analysis:

	C	*H*
calculated for $C_{23}H_{24}O_3$	79.28	6.94
found	79.24	7.07

EXAMPLE 5

Preparation of a compound of formula:



1.2 g of the compound obtained in Example 3 is dissolved in 80 cm^3 of tetrahydrofuran. The mixture is cooled to 0°C and approximately 1.5 equivalent of sulphonyldiimidazole, dissolved in tetrahydrofuran, is introduced under argon. The mixture is left at 0°C for 5 min and 10 cm^3 of ethylamine are then added. The mixture is stirred for 30 min at room temperature. The reaction mixture is washed twice with 80 cm^3 of water. The organic phase is dried over magnesium sulphate. After evaporation of the solvent and recrystallization in acetone, 670 mg of expected product are obtained, possessing the following properties:

melting point: 186–187°C

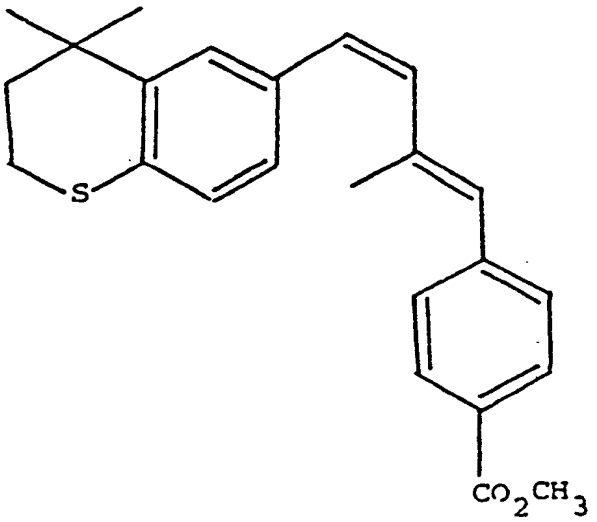
the ^1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) corresponds to the expected structure.

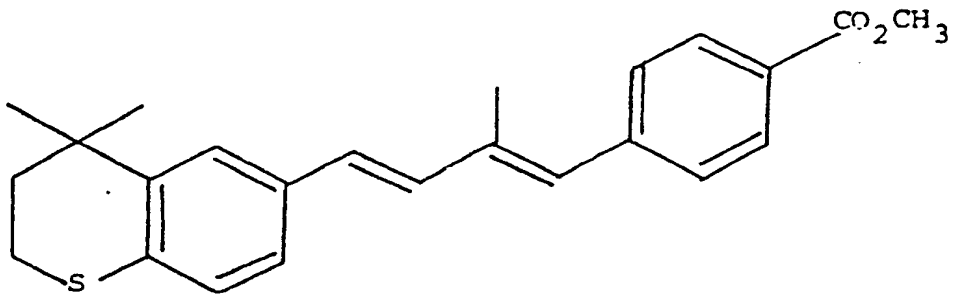
elementary analysis:

	C	*H*	*N*
calculated for $C_{25}H_{29}NO_2$	79.96	7.78	3.73
found	79.79	7.92	3.74

EXAMPLE 6

Preparation of the compounds of formulae:





These compounds are obtained according to the procedure described in Example 1c, in which [(4,4-dimethyl-6-chromanyl)methyl]triphenylphosphonoim bromide is replaced by [(4,4-dimethyl-6-thiochromanyl)methyl]triphenylphosphonium bromide. The products are obtained in an 80% yield in the form of a mixture of (Z, E) (45%) and (E, E) (55%) isomers, the proportions of which were determined by ^1H nuclear magnetic resonance.

The (E, E) isomer is isolated from the reaction mixture by crystallization, and possesses the following properties:

melting point: 110–112°C

the ^1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) is in agreement with the expected structure.

elementary analysis:

	C	*H*
calculated for $C_{24}H_{26}O_2S$	76.15	6.92
found	76.19	7.19

The (Z, E) isomer is obtained from the mother liquors of crystallization by chromatography on silica gel, using a mixture of hexane and ethyl acetate as eluant; it possesses the following properties:

melting point: 84–86°C

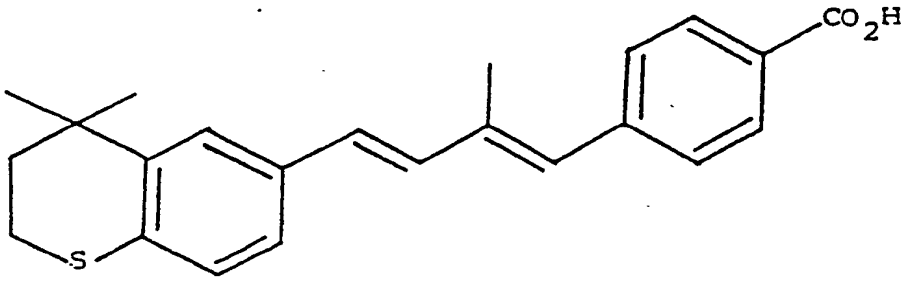
the ^1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) is in agreement with the expected structure.

elementary analysis:

	C	*H*
calculated for $C_{24}H_{26}O_2S$	76.15	6.92
found	76.20	7.13

EXAMPLE 7

Preparation of a compound of formula:



This compound is obtained according to the procedure described in Example 3, in which the compound of Example 1c is replaced by the compound of Example 6 in the form of the (E, E) isomer.

The product obtained possesses the following properties:

melting point: 178°C (with decomposition)

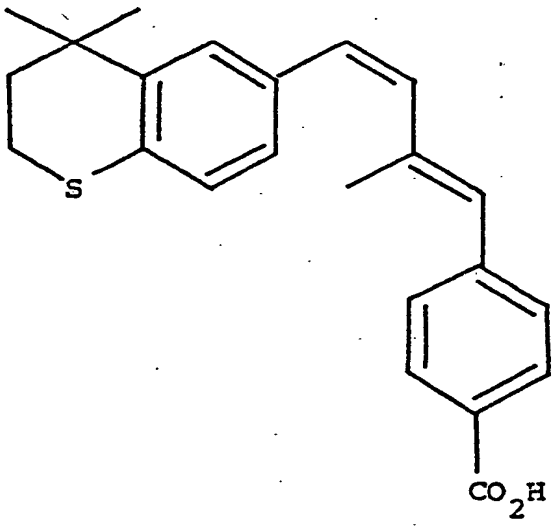
the ^1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) corresponds to the expected structure.

elementary analysis:

	C	*H*	*O*	*S*
calculated for $C_{23}H_{24}O_2S$	75.82	6.59	8.79	8.79
found	75.31	6.77	8.94	8.17

EXAMPLE 8

Preparation of a compound of formula:



This compound is obtained according to the procedure described in Example 3, in which the compound of Example 1c is replaced by the compound of Example 6 in the form of the (Z, E) isomer.

The product obtained possesses the following properties:

melting point: 160°C–165°C (with decomposition)

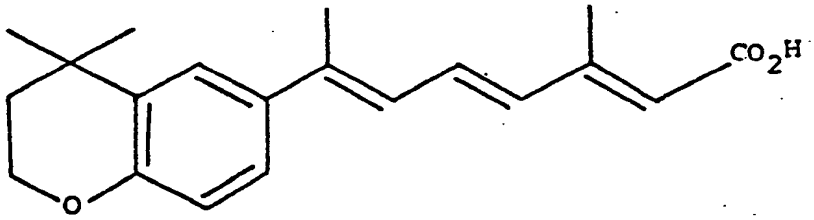
the ^1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) corresponds to the expected structure.

elementary analysis:

	C	*H*
calculated for $C_{23}H_{24}O_2S$	75.72	6.58
found	75.65	6.55

EXAMPLE 9

Preparation of a compound of formula:



a) 10.2 g of aluminium chloride are added in small portions to a solution of 12 g of 4,4-dimethylchroman and 6 g of acetyl chloride in 105 cm^3 of nitromethane under argon. After 6 hours' reaction at room temperature, 100 cm^3 of 6N hydrochloric acid are added slowly. The mixture is stirred for 10 min and 120 cm^3 of ether are then added. The organic phase is washed with water, then with saturated aqueous sodium bicarbonate solution and again with water. After the organic phase has been dried and the solvent distilled off under reduced pressure, 8.5 g of 6-acetyl-4,4-dimethylchroman are obtained.

b) A solution of 8 g of 6-acetyl-4,4-dimethylchroman in 50 cm^3 of anhydrous ether is added slowly under argon to a suspension of 6 g of lithium aluminium hydride in 150 cm^3 of anhydrous ether. The reaction mixture is left with stirring at room temperature for 20 hours. 3 cm^3 of ethyl acetate are added, followed by 10 cm^3 of 5% strength hydrochloric acid. After 5 min of stirring, the organic phase is decanted. The aqueous phase is washed twice with 150 cm^3 of ether. The organic phases are combined, then washed with 200 cm^3 of 5% strength potassium carbonate solution and then with 150 cm^3 of saturated aqueous sodium chloride solution.

After drying over sodium sulphate, the solvent is distilled off under reduced pressure. The residue is purified by crystallization in hexane. 6.3 g of 4,4-dimethyl-6-hydroxyethylchroman are obtained.

c) 10 g of triphenylphosphine are dissolved in 100 cm^3 of ether. The passage of a gaseous hydrobromic acid causes the precipitation of triphenylphosphine hydrobromide, which is filtered off and used without further purification.

A solution of 6 g of 4,4-dimethyl-6-hydroxyethylchroman and 10.3 g of triphenylphosphine hydrobromide in 250 cm^3 of methanol is stirred for 24 hours under argon. The solvent is distilled off under reduced pressure. The oily residue is washed with ether until crystallization occurs. After filtration and drying, 13.15 g of the expected phosphonium bromide are obtained.

d) The phosphonium bromide obtained above is condensed with (2E,4E)-5-ethoxycarbonyl-4-methyl-2,4-pentadien-1-al under the same conditions as those described in Example 1c. The crude product is separated from the triphenylphosphine oxide by treatment with hexane. After evaporation of the solvent, the expected product, 6-[6-ethoxycarbonyl-1,5-dimethyl-1,3,5-hexatrienyl]-4,4-dimethylchroman, is obtained in the form of a mixture of (1Z, 3E 5E) (33%) and (1E, 3E, 5E) (66%) isomers. The proportions of each of the two isomers were determined by ^1H nuclear magnetic resonance.

e) Hydrolysis of the mixture of isomeric esters obtained in 9d) is carried out according to the same procedure as that described in Example 3. After recrystallization in acetone, the expected compound of all-trans structure is obtained. It possesses the following properties:

melting point: 175°C (with decomposition)

the ^1H nuclear magnetic resonance spectrum (200 MHz, $CDCl_3$) corresponds to the expected structure.

elementary analysis:

	C	*H*
calculated for $C_{20}H_{24}O_3$	76.89	7.74
found	76.81	8.01

EXAMPLE A

Preparation of insoluble 0.5 g tablets having the following formulation:

Compound of Example 3	0.050 g
Lactose	0.082 g
Stearic acid	0.003 g
Purified talc	0.015 g
Sweetener q.s.	
Colouring q.s.	
Rice starch q.s.	0.500 g

These tablets, containing 0.05 g of active compound (compound of Example 3), are obtained by direct dry compression of the mixture of the different constituents above. The tablets are administered at the rate of 2 to 4 per day in the treatment of psoriasis.

EXAMPLE B

Preparation of a gel for topical application having the following formulation:

Compound of Example 5	0.05 g
Ethanol	43.00 g
α-tocopherol	0.05 g
Crosslinked carboxyvinyl polymer sold under the trade name "CARBOPOL 941" by "GOODRICH CHEMICAL"	0.50 g
Triethanolamine in 20% strength aqueous solution	3.80 g
Water	9.30 g
Propylene glycol q.s.	100.00 g

This gel is applied 1 to 3 times per day on a skin affected by dermatosis or a skin suffering from acne.

EXAMPLE C

Preparation of a gel for topical application having the following formulation:

Compound of Example 6	0.025 g
Erythromycin base	4.000 g
Butylated hydroxytoluene	0.050 g
Hydroxypropylcellulose sold under the trade name "KLUCEL HF" by "HERCULES"	2.000 g
Ethanol (at 95%) q.s.	100.000 g

This gel is applied 1 to 2 times per day on a skin suffering from acne.

EXAMPLE D

Preparation of a 0.3 g gelatin capsule having the following formulation:

Compound of Example 6	0.05 g
Corn starch	0.06 g
Lactose q.s.	0.3 g

The gelatin capsules used consist of gelatin, titanium oxide and a preservative; they are administered at the rate of 2 to 4 per day in the treatment of psoriasis.

EXAMPLE E

Preparation of an anti-sun cosmetic composition having the following formulation:

Compound of Example 1	1.00 g
Benzylidenecamphor	4.00 g
(C_8 to C_{18}) Fatty acid triglycerides	31.00 g
Glycerol monostearate	6.00 g
Stearic acid	2.00 g
Cetyl alcohol	1.20 g
Lanolin	4.00 g
Preservatives	0.30 g
Propanediol	2.00 g
Triethanolamine	0.50 g
Perfume	0.40 g
Demineralized water q.s.	100.00 g

EXAMPLE F

Preparation of an anti-seborrhoeic cream having the following formulation:

Polyoxyethylene stearate (40 moles of ethylene oxide) sold under the trade name "MYRJ 52" by "ATLAS"	4 g
Mixture of lauric esters of sorbitol and sorbitan, polyoxyethylenated with 20 moles of ethylene oxide, sold under the trade name "TWEEN 20" by "ATLAS"	1.8 g
Mixture of glycerol mono- and distearate sold under the trade name "GELEOL" by "GATTEFOSSE"	4.2 g
Propylene glycol	10 g
Butylated hydroxyanisole	0.01 g
Butylated hydroxytoluene	0.02 g
Cetyl/stearyl alcohol	6.2 g
Preservatives q.s	
Perhydrosqualene	18 g
Mixture of caprylic/capric triglycerides sold under the trade name "MIGLYOL 812" by "DYNAMIT NOBEL"	4 g
S-carboxymethylcysteine	3 g
Triethanolamine, 99%	2.5 g
Compound of Example 4	0.02 g
Water q.s.	100 g

EXAMPLE G

Preparation of an anti-acne cream having the following formulation:

Mixture of stearates of glycerol and polyethylene glycol (75 moles), sold under the trade name "GELOT 64" by "GATTEFOSSE"	15 g
Kernel oil polyoxyethylenated with 6 moles of ethylene oxide, sold under the trade name "LABRAFIL M 2130 CS" by "GATTEFOSSE"	8 g
Perhydrosqualene	10 g
Colouring q.s.	
Preservatives q.s.	
Perfumes q.s.	
Tioxolone	0.4 g
Polyethylene glycol 400	8 g
Purified water	58.5 g
Ethylenediaminetetraacetic acid disodium salt	0.05 g
Compound of Example 4	0.05 g

EXAMPLE H

Preparation of a hair lotion for promoting regrowth of the hair, having the following formulation:

Propylene glycol	20 g
Ethanol	34.92 g
Polyethylene glycol 400	40 g
Water	4 g
Butylated hydroxyanisole	0.01 g
Butylated hydroxytoluene	0.02 g
Compound of Example 9	0.05 g
Minoxidil	1 g

EXAMPLE I

Preparation of an anti-acne cream having the following formulation:

Polyoxyethylene stearate (40 moles of ethylene oxide) sold under the trade name "MYRJ 52" by "ATLAS"	4 g
Mixture of lauric esters of sorbitol and sorbitan, polyoxyethylenated with 20 moles of ethylene oxide, sold under the trade name "TWEEN 20" by "ATLAS"	1.8 g
Mixture of glycerol mono- and distearate	4.2 g
Propylene glycol	10 g
Butylated hydroxyanisole	0.01 g
Butylated hydroxytoluene	0.02 g
Cetyl/stearyl alcohol	6.2 g
Preservatives q.s.	
Polytetrahydrofuran dimethyl ether	18 g
Mixture of caprylic/capric triglycerides sold under the trade name "MIGLYOL 812" by "DYNAMIT NOBEL"	4 g
Compound of Example 9	0.02 g
Water q.s.	100 g

EXAMPLE J

This is an anti-acne kit comprising two parts:

a) *A gel having the following formulation is prepared:*

Ethyl alcohol	48.4 g
Propylene glycol	50 g
Crosslinked carboxyvinyl polymer sold under the trade name "CARBOPOL 940" by "GOODRICH CHEMICAL Co."	1 g
Diisopropanolamine, 99%	0.3 g
Butylated hydroxyanisole	0.05 g
Butylated hydroxytoluene	0.05 g
α-Tocopherol	0.1 g
Compound of Example 9	0.1 g

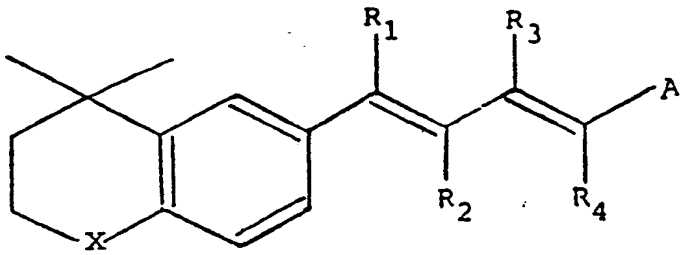
b) *A gel having the following formulation is prepared:*

Ethyl alcohol	5 g
Propylene glycol	5 g
Ethylenediaminetetraacetic acid disodium salt	0.05 g
Crosslinked carboxyvinyl polymer sold under the trade name "CARBOPOL 940" by "GOODRICH CHEMICAL Co."	1 g
Triethanolamine, 99%	1 g
Sodium lauryl sulphate	0.1 g
Purified water	75.05 g
Hydrated benzoyl peroxide, 25% strength	12.8 g

The mixing, weight for weight, of these two gels is carried out at the time required.

CLAIMS

1. A chroman or thiochroman derivative which is a compound of formula (I):



(I)

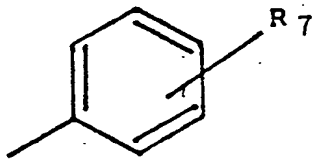
wherein:

X is –O– or –S–;

R_1, R_2, R_3 and R_4 are each, independently, hydrogen or a linear or branched C_1–C_6 alkyl group; and

A is:

a) a group of formula (II):



(II)

wherein R_7 is:

a group of formula (III):

$-CH_2OR_8$ (III)

wherein R_8 is:

hydrogen;

a C_1–C_6 alkyl group; or

a C_2–C_6 mono- or polyhydroxyalkyl group;

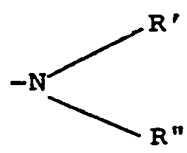
a group of formula (IV):

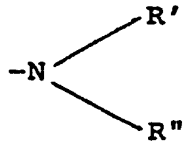
(IV)

wherein R_9 is:

hydrogen;

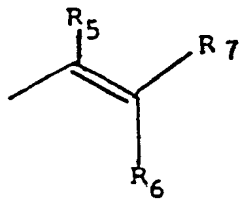
a C_1–C_6 alkyl group;

a group of formula  wherein R′ and R″ are each, independently, hydrogen, a C_1–C_6 alkyl group or a C_3–C_6 alkenyl group or wherein R′ and R″ form a heterocyclic system together with the nitrogen

atom to which they are attached, or wherein the group  is an amino acid residue or an

amino sugar residue; or
a group of formula $-O-R_{10}$, wherein R_{10} is hydrogen, a C_1–C_{20} alkyl group or a C_2–C_6 mono- or polyhydroxyalkyl group or wherein $-O-R_{10}$ is derived from a sugar; or

b) a group of formula (V)



(V)

wherein:
R_7 is as defined above; and
R_5 and R_6 are each, independently, hydrogen or a linear or branched C_1–C_6 alkyl group;
or a salt thereof, including their geometrical and optical isomers.

2. A derivative according to claim 1 wherein any C_1–C_6 alkyl groups represented by R_1, to R_6, R_8, R_9, R' and R", are each, independently, a methyl, ethyl isopropyl, butyl or tert-butyl group.

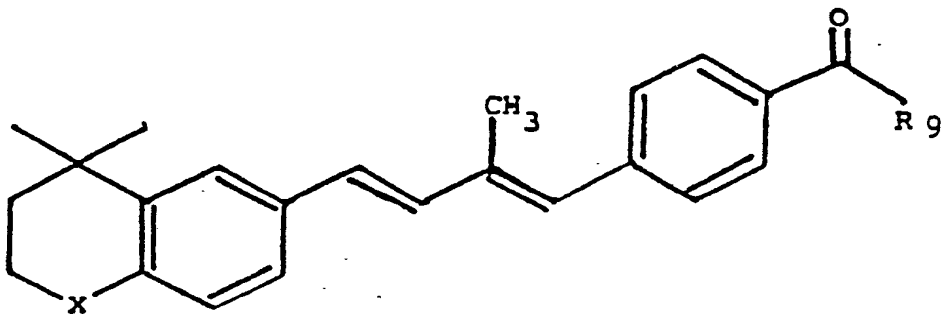
3. A derivative according to claim 1 wherein R_{10} is a methyl, ethyl, propyl, 2-ethylhexyl, octyl, dodecyl, hexadecyl or octadecyl group.

4. A derivative according to claim 1 wherein R_{10} is a 2-hydroxyethyl or 2,3-dihydroxypropyl group or a pentaerythritol residue.

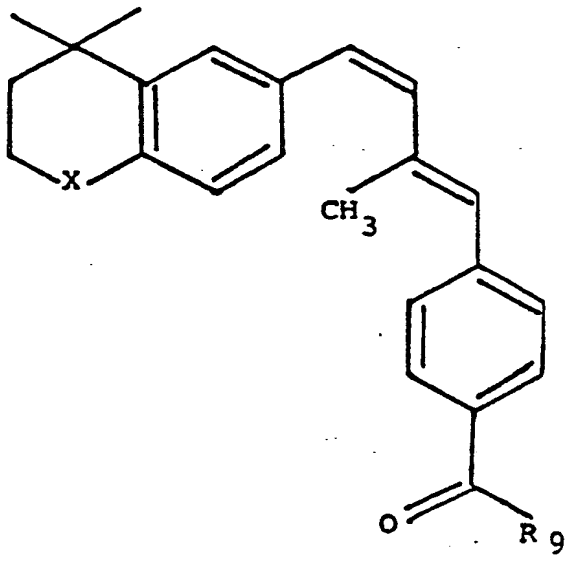
5. A derivative according to any one of claims 1 to 4 which contains at least one free acid group salified by zinc, an alkali metal or an alkaline earth metal or an organic amine or which contains at least one salified amine group.

6. A derivative according to claim 4 which contains at least one amine group salified by hydrochloride, hydrobromide or citrate.

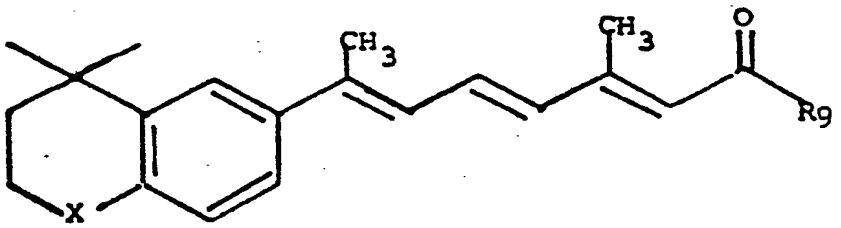
7. A derivative according to claim 1 of one of the formulae (Ia) to (Ic):



(Ia)



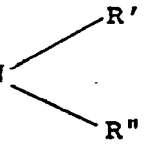
(Ib)



(Ic)

wherein:

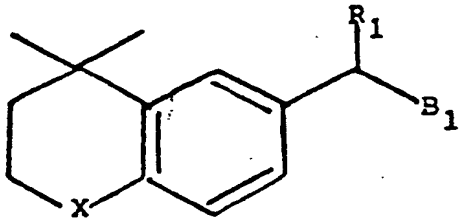
X is –O– or –S–;

R_9 is a group of formula 

wherein R′ and R″ are each, independently, hydrogen or a C_1–C_6 alkyl group or R_9 is a group of formula –O–R_{10} wherein R_{10} is hydrogen, a C_1–C_{20} alkyl group or a C_2–C_6 mono- or polyhydroxalkyl group.

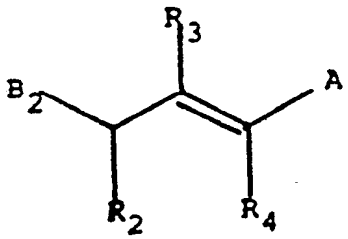
8. A derivative according to claim 7 which is:
6-[(1E,3E)-4-(4-methoxycarbonylphenyl)-3–methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1E,3E)-4-(4-methoxycarbonylphenyl)-3–methyl-1,3-butadienyl]-4,4-dimethylthiochroman;
6-[(1E,3E)-4-(4-carboxyphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1E,3E)-4-(4-carboxyphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylthiochroman;
6-[(1E,3E)-4-(4-ethylaminocarbonylphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1Z,3E)-4-(4-methoxycarbonylphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1Z,3E)-4-(4-methoxycarbonylphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylthiochroman;
6-[(1Z,3E)-4-(4-carboxyphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylchroman;
6-[(1Z,3E)-4-(4-carboxyphenyl)-3-methyl-1,3-butadienyl]-4,4-dimethylthiochroman;
6-[(1E,3E,5E)-6-ethoxycarbonyl-1,5-dimethyl-1,3,5-hexatrienyl]-4,4-dimethylchroman; or
6-[(1E,3E,5E)-6-carboxy-1,5-dimethyl-1,3,5-hexatrienyl]-4,4-dimethylchroman.

9. A process for preparing a derivative as defined in any one of claims 1 to 8 wherein a compound of formula (VI):



(VI)

is reacted with a compound of formula (VII):



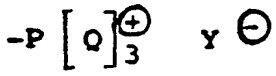
(VII)

wherein R_1, R_2, R_3, R_4 and A are as defined in claim 1 with the proviso that R_7 is not a group of formula (IV):

(IV)

when R_9 is hydrogen or a C_1–C_6 alkyl group, and wherein one of the groups B_1 and B_2 is an oxo group and the other is:

a) a triarylphosphonium group of formula (VIII):



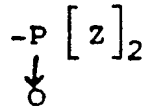
(VIII)

wherein:

Q is an aryl group; and

Y is a monovalent anion of an organic or inorganic acid; or

b) a dialkoxyphosphinyl group of formula (IX):



(IX)

wherein Z is a C_1–C_6 alkoxy group.

10. A process according to claim 9 wherein one of B_1 and B_2 is an oxo group and the other is a triarylphosphonium group of formula (VIII), wherein the reaction is performed in the presence of an alkali metal alcoholate, an alkali metal hydride, butyllithium in a solvent, an alkali metal carbonate, in an alcohol, or an alkylene oxide optionally substituted with an alkyl group, the reation temperature being from −80°C to the boiling point of the reaction mixture.

11. A process according to claim 10 wherein the reaction is performed in the presence of butyllithium in tetrahydrofuran or dimethylformamide or in the presence of an alkylene oxide optionally substituted with an alkyl group in dichloromethane.

12. A process according to claim 9 wherein one of B_1 and B_2 is an oxo group and the other is a dialkoxyphosphinyl group of formula (IX) wherein the reaction is performed in the presence of a base, the reaction temperature being from −80°C to the boiling point of the reaction mixture.

13. A process according to claim 12 wherein the reaction is performed in the presence of an inert organic solvent.

14. A process according to any one of claims 9 to 13 which further comprises subjecting the derivative obtained by reaction of the compounds of formulae (VI) and (VII) to functional modification of the substituent R_7.

15. A process according to claim 9 substantially as hereinbefore described with reference to any one of Examples 1 to 9.

16. A medicinal composition comprising at least one derivative as defined in any one of claims 1 to 8 or produced by a process as defined in any one of claims 9 to 15 and a pharmaceutically acceptable vehicle.

17. A composition according to claim 16 comprising from 2 μg to 2 mg of the chroman or thiochroman derivative per day per kg of bodyweight of the intended recipient.

18. A composition according to claim 16 or 17 suitable for enteral application in the form of a tablet, gelatin capsule, dragee, syrup, suspension, solution, powder, granules or emulsion.

19. A composition according to claim 16 or 17 suitable for parenteral application in the form of a solution or suspension for perfusion or injection.

20. A composition according to claim 16 or 17 suitable for topical application in the form of an ointment, tincture, cream, pomade, powder, patch, impregnated pad, solution, lotion, gel spray, suspension or emulsion.

21. A composition according to claim 20 which comprises from 0.0005 to 2% by weight of the chroman or

thiochroman derivative relative to the total weight of the composition.

22. A composition according to claim 16 or 17 suitable for application to the eye in the form of an eye lotion.

23. A composition according to claim 16 substantially as hereinbefore described with reference to any one of Examples A to D.

24. A cosmetic composition comprising at least one derivative as defined in any one of claims 1 to 8 or produced by a process as defined in any one of claims 9 to 15 and a cosmetically acceptable vehicle.

25. A composition according to claim 24 suitable for treatment of skin which is liable or susceptible to be affected by acne, promoting regrowth of hair, action against hair loss, combating the greasy appearance of the skin or hair, the treatment of physiologically dry skin, or treatment and prevention of the deleterious effects of sunlight.

26. A composition according to claim 24 or 25 which comprises from 0.0005 to 2% by weight of the chroman or thiochroman derivative relative to the total weight of the composition.

27. A composition according to claim 26 which comprises from 0.01 to 1% of the chroman or thiochroman derivative.

28. A composition according to any one of claims 24 to 27 in the form of a lotion, gel, cream, soap or shampoo.

29. A composition according to claim 24 substantially as hereinbefore defined with reference to any one of Examples E to J.

30. A composition according to any one of claims 16 to 29 which additionally comprises an inert, pharmacodynamically or cosmetically active additive.

31. A composition according to claim 30 wherein the additive is a moisturizing agent, anti-seborrhoeic agent, anti-acne agent, antibiotic, agent promoting regrowth of the hair, anti-inflammatory agent, carotenoid, anti-psoriatic agent, flavour-improving agent, preservative, stabilizer, moisture-regulating agent, pH-regulating agent, osmotic pressure-modifying agent, emulsifier, UV-A and/or UV-B filter or antioxidants.

32. Use of a derivative as defined in claim 1 or of a composition as defined in claim 16 in a method of treatment of the human or animal body by therapy.

33. Use of a derivative as defined in claim 1 or of a composition as defined in claim 16 in a method of treatment of a dermatological condition linked to a disorder of keratinization (differentiation, proliferation), dermatological or other condition having an inflammatory and/or immuno-allergic component, a benign or malignant, severe or extensive dermatological proliferation, epidermolysis bullosa dystrophica, a disease involving molecular changes in collagen, an ultraviolet-induced carcinoma (solar carcinogenesis), epidermodysplasia verruciformis and related forms, a rheumatoid condition, psoriatic rheumatism, atopy or in a treatment of an ophthalmological nature.

34. Use of a derivative as defined in claim 1 in the manufacture of a medicament for the treatment of a disorder as defined in claim 32.

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